Observational studies to improve clinical outcomes

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Definition

• All Non-RCTs are observational studies
Main types

• Cohort studies
• Case-control studies
• Cross-sectional studies
• Clinical audits
• Systematic reviews of observational studies
RCTs are the gold standard

What about the rest?

Waste of time??
Observational studies that have improved our health
n England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, from a quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 1,287, or roughly fifteenfold. This remarkable increase is, whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

Possible Causes of the Increase
Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust
Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack

Age: 50 years
Gender: Female
Total Cholesterol: 200 mg/dL
HDL Cholesterol: 100 mg/dL
Smoker: No
Systolic Blood Pressure: 130 mm/Hg

Are you currently on any medication to treat high blood pressure. Yes

Calculate Your 10-Year Risk

Risk Score* Less than 1%
Means less than 1 of 100
Framingham heart study
Massachusetts, USA

• 1948: Project to identify risk factors for heart disease

• Established after the death of President Roosevelt, from cerebral haemorrhage with a BP of 300/190 mmHg

• Observational study: Prospective Cohort

• Mahmood et al. The Framingham Heart study, Historical perspective, Lancet, 2014
• 5,200 Healthy Men and Women between 30-62 Years

• Their children and grand children: currently 3\textsuperscript{rd} generation

• Current sample size: approximately 15000

• Mahmood et al. The Framingham Heart study, Historical perspective, Lancet, 2014
Because of Framingham study

- We know that high BP increases the risk of heart disease
- Cigarette smoking increases the risk of heart disease
- LDL cholesterol increases the risk
- HDL Cholesterol decreases the risk
• Want a more recent example?
IARC Monographs evaluate consumption of red meat and processed meat
A Working Group of 22 experts from 10 countries convened by IARC

• Based on a review of >800 research papers
  
  • Processed meat: carcinogenic to humans (Group 1)
    • Colorectal cancer
  
  • Red meat as probably carcinogenic to humans (Group 2A)
    • Colorectal cancer
    • Pancreatic cancer
    • Prostate cancer

  • “The most influential evidence came from large prospective cohort studies”.
Association: Yes
Cause and effect: Not sure
Awareness: Yes
Controversy: Some people have labelled it Bacon-gate!!!
Carcinogenicity of consumption of red and processed meat
Safe to Sleep®
Public Education Campaign
Led by the Eunice Kennedy Shriver National Institute of Child Health and Human Development
in collaboration with other organizations

Home | About SIDS/Safe Infant Sleep | Campaign Materials | Explore the Campaign
---|---|---|---
Home

Babies Sleep Safest on Their Backs

20th Anniversary Safe to Sleep turns 20

Resource Kit
Prone position increases the risk of SIDS


• Dwyer T. Prospective cohort study of prone sleeping position and SIDS. Lancet. 1991 Tasmania, Australia

• Dwyer T et al. Prone sleeping position and SIDS: evidence from case-control and cohort studies in Tasmania. JPCH, 1991
Australia. SIDS 1981-2007
Over the last ten years an average of 100 deaths per annum
Source: Australian Bureau of Statistics
INFLUENCE OF LIGHT ON THE HYPERBILIRUBINÆMIA OF INFANTS


GENERAL HOSPITAL, ROCHFORD, ESSEX, United Kingdom
• The sister of the unit had observed

  • Fading away of yellow pigmentation in the skin of jaundiced babies

    • When they had been a short time in the sun

• Their team conducted an observational study

• Exposed jaundiced babies and measured serial bilirubin
<table>
<thead>
<tr>
<th>Case number</th>
<th>Bilirubin before sunlight treatment (mg/dl)</th>
<th>Duration of exposure Hours</th>
<th>Bilirubin after sunlight therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>19</td>
<td>4</td>
<td>15</td>
</tr>
</tbody>
</table>
Jaundice quickly disappeared from the exposed areas of skin but persisted in areas which remained in the shade.

![Graph showing 2-hour periods of sunshine](image)

![Graph showing serum bilirubin levels](image)

**Fig. 5**—Sunshine treatment of an icteric infant with jaundice of prematurity (case 6).
Fig. 6—Artificial-light apparatus for cradle illumination of infants.
35 years after introduction of phototherapy, there were two RCTs

• **Bryla DA**, *RCT of phototherapy for neonatal hyperbilirubinemia*. *Pediatrics* 1985

The first RCT of sunlight for jaundice

Slusher et al, Pediatrics, 2014
Safe and efficacious

Hospital setting

Slusher et al, Pediatrics, 2014
Is Chronic Lung Disease in Low Birth Weight Infants Preventable? A Survey of Eight Centers

Mary Ellen Avery, MD, William H. Tooley, MD, Jacob B. Keller, MPH, Suzanne S. Hurd, PhD, M. Heather Bryan, MD, Robert B. Cotton, MD, Michael F. Epstein, MD, Pamela M. Fitzhardinge, MD, Cheryl B. Hansen, RN, Thomas N. Hansen, MD, W. Alan Hodson, MD, L. Stanley James, MD, Joseph A. Kitterman, MD, Heber C. Nielsen, MD, Theresa A. Poirier, RN, William E. Truog, MD, and Jen-Tien Wung, MD

From Brigham and Women’s Hospital, Boston; University of California, San Francisco; National Heart, Lung, and Blood Institute, Bethesda; Mt Sinai Hospital, Toronto; Vanderbilt University, Nashville, TN; Baylor University, Houston; University of Washington, Seattle; Columbia Presbyterian Medical Center, New York; and Southwestern Medical School, Dallas
Survivors to 28 days

Centre 3, Columbia had the lowest incidence of CLD and highest use of CPAP.

**Figure.** Shaded areas are percentages of infants in oxygen at 28 days of age; open areas are survivors without added oxygen at 28 days. Note that center 3 has lowest percentage of infants who were dependent on oxygen and among the highest percentage of survivors.
Majority of the NICUs use CPAP even in tiny babies now
Congenital diaphragmatic hernia registry, 66 centres from all over the world

8279 patients in the database

Harting and Lally, Seminars in neonatal medicine, 2014
Because of the CDH registry, we know that

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean section</td>
<td>Probably unnecessary</td>
</tr>
<tr>
<td>ECMO</td>
<td>Probably useful</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Probably not necessary</td>
</tr>
<tr>
<td>Prematurity</td>
<td>High mortality</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>30%</td>
</tr>
</tbody>
</table>

Note the word “**Probably**” because the results are from observational data.
Observational studies

• Can enable change in practice
• Can generate hypothesis for RCTs
• Provide benchmarking
• Can create controversy!!
• Do the results of observational studies correlate with RCTs?
Concordance between Observational studies and RCTs

- Forty-five diverse topics were identified
  - For which both RCTs (n = 240) and non-RCTs (n = 168) had been performed
- Very good correlation between the odds ratios of RCTs and non-RCTs
  - $r = 0.75; P<.001$

- Ioannidis, JAMA, 2001

Stanford University
• Ioannidis, JAMA, 2001

X axis: Odds ratios in RCTs

Y Axis: Odds ratios in observational studies
Concordance between Observational studies and RCTs

Yale University

Before we get too excited about observational studies
For each 10 ng/mL increment in baseline Vitamin D levels, the risk of hypertension decreased by 12%

Kunutsor et al, Eur J Epidemiology, 2013

What did the RCTs find?
Meta analysis of RCTs

- 46 RCTs
- 4500 participants
- No benefit of vitamin D supplementation

- SBP: Mean difference: 0 (95% CI: -0.8, 0.8) mm Hg
- DBP: Mean difference: -0.1 [95% CI, -0.6 to 0.5] mm Hg

*Beveridge, JAMA Intern Med. 2015 May*
RCTs are the gold standard

Just to remind ourselves
It is also important to know that

• “A well designed observational study is preferable to a poorly designed RCT”

• Britton A, Health Technology assessment, 1998
• Observational studies are used quite extensively in surgical field

• Reason: Surgical RCTs are challenging/difficult

Randomised trials in surgery: problems and possible solutions.

McCulloch P¹, Taylor I, Sasako M, Lovett B, Griffin D.
Challenges in performing surgical randomized controlled trials in Japan.
Sasako M, Kurokawa Y.

Challenges of randomized controlled surgical trials.
Campbell AJ, Bagley A, Van Heest A, James MA.

Studying surgical innovations: challenges of the randomized controlled trial.

Unger CA¹, Barber MD².
If surgical RCTs are challenging and rare

• Options

  • Strive Hard to promote RCTs

  • At the same time, conduct good quality observational studies

  • I will give some of our observational studies that have improved outcomes for our babies
We had very high incidence of VP shunt infections

<table>
<thead>
<tr>
<th>Year</th>
<th>2002-2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF Shunt Infections</td>
<td>6/23 (26%)</td>
</tr>
</tbody>
</table>

We were desperate
Antibiotic impregnated VP shunts: Meta analysis of observational studies

- 12 studies (paediatric, adult and neonate)
- Only one was RCT

Thomas, Lee, Patole & Rao, British Journal of Neurosurgery, 2011
Antibiotic impregnated catheters have reduced the incidence of CSF shunt infections in our unit

<table>
<thead>
<tr>
<th>Year</th>
<th>2002-2006</th>
<th>2007-2015</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF Shunt infections</td>
<td>6/23 (26%)</td>
<td>1/26 (4%)</td>
<td>We don’t mind!!</td>
</tr>
</tbody>
</table>
Ward reduction of gastroschisis: retrospective study
# Ward reduction of gastroschisis: retrospective study

<table>
<thead>
<tr>
<th></th>
<th>Ward reduction N=11</th>
<th>Silo or reduction under GA N=27</th>
<th>Odds Ratio</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iatrogenic Necrosis of bowel</td>
<td>27%</td>
<td>4%</td>
<td>10.7</td>
<td>0.08</td>
</tr>
<tr>
<td>TPN&gt;60 D</td>
<td>18%</td>
<td>4%</td>
<td>4.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Unplanned return to theatre</td>
<td>27%</td>
<td>7%</td>
<td>3.9</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Rao SC, J Paediatr Child Health. 2009*
• We stopped doing ward reductions

• We use silo reduction

• Since the past five years (n=50),
  • No case of iatrogenic gut necrosis
  • No case of unplanned return to theatre
Surgical management of perforated NEC

• We had noticed that

  • Preterm infants undergoing primary peritoneal drainage for NEC Perforation had high morbidity

• Hence, we did an observational study

• (Retrospective cohort)
Peritoneal drainage versus laparotomy for perforated necrotising enterocolitis or spontaneous intestinal perforation: A retrospective cohort study

Abhijeet Rakshasbhuvankar, Shripada Rao, Corrado Minutillo, Ian Gollow and Satish Kolar
<table>
<thead>
<tr>
<th></th>
<th>Primary peritoneal drainage</th>
<th>Primary laparotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=19</td>
<td>N=20</td>
</tr>
<tr>
<td>Median gestational age (w)</td>
<td>24.7</td>
<td>25.2</td>
</tr>
</tbody>
</table>
Results

Study cohort  
\( n = 39 \)

- **NEC**  
  \( n = 25 \)
  - PD  
    \( n = 9 \)
    - Mortality  
      \( n = 8 \) (88.8%)
  - Laparotomy  
    \( n = 16 \)
    - Mortality  
      \( n = 7 \) (43.7%)

- **SIP**  
  \( n = 14 \)
  - PD  
    \( n = 10 \)
    - Mortality  
      \( n = 2 \) (20%)
  - Laparotomy  
    \( n = 4 \)
    - Mortality  
      \( n = 0 \) (0%)

\( p = 0.04 \)

\( p = 1.00 \)
Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis or spontaneous intestinal perforation in preterm low birth weight infants (Review)

Rao SC, Basani L, Simmer K, Samnakay N, Deshpande G

Insufficient sample size; 2 RCTS, 195 babies; No firm recommendations; RCTs are needed

Rao, Basani, Simmer, Samnakay, Deshpande, 2012
## Meta analysis of RCTs and observational studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PD Events</th>
<th>Total</th>
<th>LAP Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moss rct 2006</td>
<td>19</td>
<td>55</td>
<td>22</td>
<td>62</td>
<td>28.3%</td>
<td>0.96 [0.45, 2.05]</td>
</tr>
<tr>
<td>Tepas prosp/cohort 2006</td>
<td>14</td>
<td>33</td>
<td>12</td>
<td>32</td>
<td>14.6%</td>
<td>1.23 [0.45, 3.32]</td>
</tr>
<tr>
<td>Rees rct 2008</td>
<td>14</td>
<td>35</td>
<td>11</td>
<td>33</td>
<td>14.2%</td>
<td>1.33 [0.50, 3.59]</td>
</tr>
<tr>
<td>Blakely prosp/cohort 2005</td>
<td>43</td>
<td>80</td>
<td>33</td>
<td>76</td>
<td>32.7%</td>
<td>1.51 [0.81, 2.85]</td>
</tr>
<tr>
<td>Moss prosp cohort, 2006</td>
<td>29</td>
<td>70</td>
<td>7</td>
<td>47</td>
<td>10.2%</td>
<td>4.04 [1.59, 10.28]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>119</strong></td>
<td><strong>273</strong></td>
<td><strong>250</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.55 [1.08, 2.22]</strong></td>
<td></td>
</tr>
</tbody>
</table>

- **Total events**: 119
- **Heterogeneity**: $\chi^2 = 5.88$, df = 4 ($P = 0.21$); $I^2 = 32\%$
- **Test for overall effect**: $Z = 2.38$ ($P = 0.02$)

---

Peritoneal drainage was associated with increased odds of mortality

**Sola et al, J Surg Res. 2010**
• We rarely do primary peritoneal drainage as a definitive treatment

• Our outcomes have been better (an audit is underway)
Current situation

• Nine of ten publications describe observational research

  Von Elm, BMJ, 2007

• RCTs constitute less than 5% of all biomedical articles

  John Ioanidis, Lancet 2014

• 9 of 10 research papers published are observational

  Stefania Boccia, Eur J Public Health. 2015
What it means?

• Whether we like it or not, observational studies are here to stay

• It is better to improve the quality of conduct and reporting
Use STROBE guidelines for reporting observational studies

• The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement

Epidemiology. 2007
Use MOOSE guidelines for reporting Meta analyses of observational studies

- Meta-analysis Of Observational Studies in Epidemiology (MOOSE)

JAMA. 2000 Apr 19
### Essential resources for writing and publishing health research

#### Library for health research reporting

The Library contains a comprehensive searchable database of reporting guidelines and also links to other resources relevant to research reporting.

- **Search for reporting guidelines**
- **Not sure which reporting guideline to use?**
- **Reporting guidelines under development**
- **Visit the library for more resources**

#### Reporting guidelines for main study types

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Guideline</th>
<th>Extensions</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised trials</td>
<td>CONSORT</td>
<td>Extensions</td>
<td>Other</td>
</tr>
<tr>
<td>Observational studies</td>
<td>STROBE</td>
<td>Extensions</td>
<td>Other</td>
</tr>
<tr>
<td>Systematic reviews</td>
<td>PRISMA</td>
<td>Extensions</td>
<td>Other</td>
</tr>
<tr>
<td>Case reports</td>
<td>CARE</td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Qualitative research</td>
<td>SRQR</td>
<td>COREQ</td>
<td>Other</td>
</tr>
<tr>
<td>Diagnostic / prognostic studies</td>
<td>STARD</td>
<td>TRIPOD</td>
<td>Other</td>
</tr>
<tr>
<td>Quality improvement studies</td>
<td>SQUIRE</td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Economic evaluations</td>
<td>CHEERS</td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Animal pre-clinical studies</td>
<td>ARRIVE</td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Study protocols</td>
<td>SPIRIT</td>
<td>PRISMA-P</td>
<td>Other</td>
</tr>
</tbody>
</table>
Conclusions

• Do not despair if you cannot do an RCT

• Well designed observational studies can improve outcomes

• Need to be conducted with the same rigour as RCTs

• Know the strengths and limitations of observational studies

• Should be considered as complimentary, not rival to RCTs

• Ligthelm, R, Clinical therapeutics, 2007
Thank you